

**REMARKS**

Claims 1, 9, 13, 15, and 19-24 are pending in the application.

Claim 1, the sole independent claim, recites a therapeutic treatment for a human suffering from Alzheimer's disease by administering a therapeutically effective amount of an endothelin antagonist recited in the claim. In particular, the present invention is *not* directed to a cure for Alzheimer's disease. A person suffering from Alzheimer's disease will not be freed from the disease by the present method. The present method *does* treat adverse effects or symptoms resulting from Alzheimer's disease by addressing the issue of a reduced blood flow to the brain caused by Alzheimer's disease. The present method overcomes the vasoconstriction associated with Alzheimer's disease and improves a blood flow in the brain. This difference between cure and treatment must be kept in mind when considering the patentability of the presently claimed method because statements in the Office Action appear to equate cure and treatment.

Claim 9 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite because of a lack of antecedent basis in claim 1 for the transitional phrase "comprising". In response, applicants have amended claim 9 to recite "is" in place of "comprising". In view of the amendment to claim 9, it is submitted that amended claim 9 fully complies with 35 U.S.C. §112, and that the rejection should be withdrawn.

Claims 1 and 9 stand rejected under 35 U.S.C. §103 as being obvious over Hughes et al. U.S. Patent Publication 2003/0040534 ('534) in view of a Wu publication (Wu). Claims 13, 15, and 19-24 stand rejected under 35 U.S.C. §103 as being obvious over the '534 publication in view of Wu, and further in view of Woolf U.S. Patent No. 5,466,696 ('696). For the reasons set forth below, it is submitted that these rejections are in error and should be withdrawn.

The '534 publication discloses a specific endothelin antagonist, wherein the (+) dextrorotatory atropisomer has a much higher potency than the (-) levorotary atropisomer or the racemate ('534 publication, abstract). The '534 publication also discloses that the compounds are antagonists of ET-1, ET-2, and/or ET-3 and are useful in treatment of

conditions associated with increased ET levels and all endothelin-dependent disorders ('534 publication, paragraph [0011]).

The '534 publication then recites a myriad of conditions that may be treated using the disclosed endothelin antagonist of the '534 publication ('534 publication, paragraphs [0012] through [0018]). The '534 publication provides data showing *in vitro* binding of the enantiomers of the compound. The '534 publication, however, fails to tie this binding to *any*, let alone *all*, of the diseases and conditions set forth at paragraphs [0012]-[0018] of the reference.

It also is important to note that the '534 publication generalized the use of an endothelin inhibitor in the treatment of *any* endothelin related disorder. However, it is widely known that there are two types of endothelin receptors, ET<sub>A</sub> and ET<sub>B</sub> (Yanagisawa et al., 1988). It also is well known that ET<sub>A</sub> receptors are potent vasoconstrictors (Feuerstein et al., 1994; Sagher et al., 1994).<sup>1)</sup> In contrast, ET<sub>B</sub> receptors are well known as potent vasodilators (Eddahibi et al., 1993; Ekelund et al., 1994; Kitazono et al., 1995). Hence, ET<sub>A</sub> and ET<sub>B</sub> receptors act opposite to one another (Yanagisawa and Masaki, 1989).

Studies have shown that, even in the central nervous system, the response of ET<sub>A</sub> and ET<sub>B</sub> receptors is different. ET<sub>A</sub> receptors produce cardiovascular effects, whereas ET<sub>B</sub> receptors do not produce cardiovascular effects (Gulati et al., 1997). Examples wherein one type of endothelin receptor is involved, and the other is not, are numerous. One example related to aging is that aging results in an augmented gastrocnemius muscle arteriolar vasoconstriction to ET-1. This vasoconstriction is mediated through an enhanced ET<sub>A</sub> receptor signaling pathway and not through an ET<sub>B</sub> receptor mechanism (Donato et al., 2005). Another example is a study conducted on 191 healthy middle-aged and older (65+/-1 years) human subjects to clarify the relationship between the regular exercise-induced improvement of arterial stiffness and the gene polymorphisms of ET converting enzyme (ECE)-1, ECE-2, ET<sub>A</sub> receptor (ET<sub>A</sub>), and ET<sub>B</sub> receptor (ET<sub>B</sub>). The results suggest that differences in ET<sub>A</sub> and ET<sub>B</sub> polymorphisms may influence the response of the vascular wall

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<sup>1</sup> See Appendix for full cites. A copy of each publication cited in the Appendix is submitted concurrently with this Amendment.

to exercise, whereas ECE-1 polymorphisms may affect basal blood pressure (Iemitsu et al., 2006).

Thus, it is well known that inhibition of ET<sub>A</sub> receptor or ET<sub>B</sub> receptors, or both, can produce different effects. The '534 publication discloses the use of CHC-K1 cell expressing ET<sub>A</sub> receptors (paragraphs [0033]-[0037]). The reference therefore demonstrates binding of the disclosed compound to ET<sub>A</sub> receptors, but not to ET<sub>B</sub> receptors.

In addition, the '534 publication states that the disclosed compounds "are antagonists of ET-1, ET-2 *and/or* ET-3" (paragraph 11, emphasis added). The '534 publication therefore does *not* disclose ET-1, ET-2, and ET-3 antagonism, but the *possibility* of ET-1, ET-2, and ET-3 antagonist. The reference enable no more than ET<sub>A</sub> receptor antagonism.

In addition, and importantly, the '534 publication has merely demonstrated *binding* of the disclosed compound to ET<sub>A</sub> receptors. The reference provides no teaching as to whether the compound is an agonist or an antagonist of ET<sub>A</sub>. Accordingly, the compound of the '534 publication may inhibit or may *activate* ET<sub>A</sub>. The reference provides no guidance and it cannot be concluded that the compound inhibits ET<sub>A</sub>. The reference provides absolutely no guidance with respect to ET<sub>B</sub> receptors, or even that the disclosed compounds can bind to ET<sub>B</sub> receptors. The presently claimed compounds are known as ET<sub>A</sub>/ET<sub>B</sub> inhibitors and are useful in the treatment Alzheimer's disease symptoms and adverse effects.

The present claims recited mixed ET<sub>A</sub>/ET<sub>B</sub> antagonists, i.e., compounds that antagonize both ET<sub>A</sub> and ET<sub>B</sub>, e.g., bosentan of claim 9. The '534 publication teaches an ET<sub>A</sub> antagonist. The '534 publication fails to teach that the disclosed compound is a mixed ET<sub>A</sub>/ET<sub>B</sub> antagonist, and provides a person skilled in the art no incentive or apparent reason to substitute a mixed ET<sub>A</sub>/ET<sub>B</sub> receptor antagonist for an ET<sub>A</sub> receptor antagonist disclosed in the reference. What would motivate a person skilled in the art administer a mixed ET<sub>A</sub>/ET<sub>B</sub> antagonist, when such antagonism results in opposite effects? This is especially the case after considering ET<sub>A</sub> receptor antagonist disclosed in the '534 publication.

Furthermore, the '534 publication purports a treatment of the diseases disclosed in paragraphs [0012]-[0018]. As stated above, the present invention is not directed to a treatment of Alzheimer's disease, but to treating the adverse effects or symptoms resulting for Alzheimer's disease.

The Wu reference does not overcome the deficiencies of the '534 publication with respect to using an endothelin antagonist recited in the claims to treat Alzheimer's disease in a human. The Wu reference is relied upon for a teaching of various endothelin antagonists, and that bosentan is in clinical trials. First, it must be noted that bosentan is *not* in clinical trials relating to Alzheimer's disease. The fact that bosentan is in clinical trials is irrelevant with respect to the claims at issue.

Wu is a review article that teaches, identifies, and classifies various endothelin antagonists. Notably, Wu does *not* teach or suggest the use of an endothelin antagonist in the treatment of Alzheimer's Disease. A person skilled in the art, even with the '534 publication and the Wu reference before him, still would not have had any apparent reason to make the leaps in reasoning discussed above with respect to the '534 publication and thereby arrive at the presently claimed invention. At most, a person skilled in the art would substitute an ET<sub>A</sub> antagonist disclosed in the Wu reference for the compound disclosed in the '534 publication. Even a substitution of an ET<sub>A</sub> antagonist of Wu into the '534 publication would not overcome the deficiencies of the '534 publication in rendering the present claims obvious.

In summary, for all of the reasons set forth above, it is submitted that present claims 1 and 9 also are patentable over a combination of the '534 publication and the Wu reference. Accordingly, this rejection of claims 1 and 9 under 35 U.S.C. §103 should be withdrawn.

With respect to the rejection of claims 13-15 and 19-24 over a combination of the '534 publication, Wu, and the '696 patent, the examiner relies upon the '696 patent for a teaching that cholinesterase inhibitors are known to treat dementias. Claims 13-15 and 19-24 recite preferred embodiments of the present invention. However, applicant does not rely upon the administration of a cholinesterase inhibitor to treat AD as the sole point of patentability.


Applicant relies upon all the features recited in claims 13, 15, and 19-24 *and* the claims from which they depend, including claim 1, for patentability. The '696 patent fails to overcome the deficiencies of the '534 publication and Wu with respect to treating a human suffering from Alzheimer's Disease with an endothelin antagonist. Therefore, claims 13-15 and 19-24 are patentable over a combination of the '534 publication, Wu, and the '696 patent, for the same reasons claims 1 and 9 are patentable over a combination of the '534 publication and Wu. Accordingly, the rejection of claims 13, 15, and 19-24 under 35 U.S.C. §103 should be withdrawn.

It is submitted that the claims are now in a form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

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Respectfully submitted,

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## Appendix

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